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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/785,497	02/24/2004	Mark W. Becker	249.P2	9922

25000 7590 04/24/2008

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EXAMINER	
MARTIN, PAUL C	

ART UNIT	PAPER NUMBER
1657	

MAIL DATE	DELIVERY MODE
04/24/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/785,497	**Applicant(s)** BECKER ET AL.	
	Examiner PAUL C. MARTIN	**Art Unit** 1657	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 07 April 2008 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☐ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☐ The period for reply expires _____months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☒ The Notice of Appeal was filed on *07 April 2008*. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1, 3-13 and 15-17*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: see attached.
12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

/Jon P Weber/, SPE 1657

Claim Rejections - 35 USC § 103

Claims 1, 3-7 and 10-13 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Shaw et al. (1997) for reasons of record set forth in the Prior Action.

Claims 1, 3-7, 9-13, 15 and 16 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Shaw et al. (1997) in view of Glazier et al. (US 5,627,165) for reasons of record set forth in the Prior Action.

Claims 1, 3-8, 10-13 and 17 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Shaw et al. (1997) in view of Starrett et al. (US 5,663,159) for reasons of record set forth in the Prior Action.

Response to Arguments

Applicant's arguments filed 04/07/08 have been fully considered but they are not persuasive.

The Applicant argues that Shaw et al. are concerned with determining oral bioavailability of test compound, were not concerned with relative tissue distribution of the cleavage product and did not have the objective the determination of differential antiviral activity in the tissues being sampled as they were simply looking at the stability of the prodrugs to hydrolysis (Remarks, Pg. 5, Lines 13-19).

This is not found to be persuasive for the following reasons, there is no indication in the currently pending claims that Applicant was concerned with the relative distribution of the cleavage products, Applicant is only concerned with determining the antiviral or antitumor activity in the tissues and/or amount of at least one metabolite of the prodrug in the tissues. As discussed in the Prior Actions, as discussed in the prior office action repeated below, Shaw et al. teaches every step of the claimed invention comprising the steps of; providing an amino acid phosphonoester prodrugs of PMPA (Pg. 1825, Table 1), selecting a target tissue (plasma) and non-target tissues (liver and intestine), administering the prodrug to both tissues and determining the relative in vitro biological stability and bioavailability of PMPA in the tissues (Pg. 1827, Column 1, Lines 7-8 and Column 2, Lines 1-14 and Table 3, and Pg. 1828, Column 1, Lines 1-10).

Shaw et al. teaches wherein the prodrug of PMEA was shown to significantly increase the oral bioavailability of PMEA in HIV infected patients and wherein PMPA has selective and potent inhibitory activity in vitro against retroviruses and wherein IV PMPA has been shown to reduce viral load in HIV infected patients (Pg. 1824, Column 2, Lines 1-9 and 16-18).

Shaw et al. teaches the administration of the PMPA prodrug to live dogs and the determination of the relative activity by analysis of the animal tissue after administration of the prodrug, wherein the activity is determined the amount of PMPA in the tissue (Pg. 1827, Fig. 2).

As discussed previously, it is inherent in the method of Shaw et al. that the screening method would determine the relative antiviral activity conferred by the PMPA prodrug in the target and non-target tissues because PMPA is a known potent antiviral compound and the determination of the biological stability and bioavailability of prodrug derived PMPA in various tissues would necessarily also provide a determination of the relative antiviral activity of the prodrug in those tissues even if no virus were present in the tissues. That the Applicant has recognized another advantage (relative tissue distribution) which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See Ex parte Obiaya, 227 USPQ 58, 60 (Bd. Pat. App. & Inter.1985).

The Applicant argues that Shaw et al. fails to meet the target tissue limitation because plasma is allegedly not a tissue and the Examiner's argument that it would have been obvious to use blood instead of plasma is no based upon any cited reference. Applicant further argues that as blood contains cells which have a unique complement of esterolytic enzymes not found in plasma and references a citation allegedly showing that blood and plasma do not produce equivalent hydrolytic profiles against a target ester (Remarks, Pg. 5, Lines 20-24 and Pg. 6, Lines 1-8).

This is not found to be persuasive for the following reasons, the Office does not have to provide references supporting arguments as long as the basis for rejection is either a fact and/or technical reasoning to reasonably support the determination of obviousness. As discussed in the Prior action, Shaw et al. teaches the administration of the prodrug PMPA to plasma and to tissue homogenates of liver and intestine. In plasma, intestine and liver, the PMPA and prodrug compounds are shown to be enzymatically (esterase) degraded over time. As plasma is blood plasma with the cells removed (monocytes, macrophages, etc) but with the enzyme components remaining, one of ordinary skill in the art would have concluded that the degradation observed in plasma would have been the same in whole blood. Therefore, plasma and whole blood would have been recognized as functionally equivalent as they would provide equivalent results. One of ordinary skill in the art would certainly have recognized that whole blood and liver homogenates were different tissues as defined in the instant specification. As to Applicant's reference, the Office would be happy to consider any reference when properly submitted.

The Applicant argues that the claims are distinguishable from Shaw et al. in that they exclude intestine as a target tissue, and that Shaw et al. contain no teaching or suggestion to exclude intestinal homogenate from their study (Remarks, Pg. 6, Lines 9-15).

This is not found to be persuasive for the following reasons, as discussed in the prior action, Shaw et al. teaches providing an amino acid phosphonoester prodrugs of PMPA (Pg. 1825, Table 1), selecting a target tissue (plasma) and non-target tissues (liver and intestine), administering the prodrug to both tissues and determining the relative in vitro biological stability and bioavailability of PMPA in the tissues. As the Applicants broad claim is drawn only to selecting at least one target tissue and at least one non-target tissue, wherein the target tissue and non-target tissues are not the same and wherein the target tissue does not include small intestine, the reference still

makes obvious the claims as plasma and liver homogenate meet the instant claim limitations of being at least one target tissue and at least one non-target tissue, wherein the target tissue and non-target tissues are not the same and wherein the target tissue does not include small intestine. That Applicant has specifically stated that intestinal tissue cannot be used in the instant invention does not serve to non-obviate the teachings of the reference.

The Applicant argues that the Shaw et al. references administration of prodrugs to live dogs does not render claim 10 obvious because Shaw et al. were simply determining the ability of the prodrug to produce active drug in the circulation after oral administration and do not disclose administering the prodrug and then assaying conversion to parental drug in target vs. non-target tissues wherein Applicant's method contemplates determining differential activity in various tissues (Remarks, Pg. 6, Lines 16-21).

This is not found to be persuasive because, as discussed above, Shaw et al. teaches the administration of the PMPA prodrug to live dogs and the determination of the relative activity by analysis of the animal tissue after administration of the prodrug, wherein the activity is determined the amount of PMPA in the tissue. In this case, the adaptation of the method of Shaw et al. for screening prodrug levels in plasma and tissue homogenates to screening for prodrug levels in intact animals and/or tissues derived therefrom would have been obvious to one of ordinary skill in the art because based upon scientific reasoning: Intact animals are more complex and variable systems than cell homogenates and the translation of in vitro methods to in vivo applications is well-known to those of ordinary skill in the art at the time of the instant invention.

The Applicant argues that nothing but hindsight motivates the rejection of Claim 10, as it is far less trouble to measure prodrug stability in tissue homogenates than in intact animals and the Examiner has not provided credible evidence for the assertion that other variables would direct the change. Applicant further asserts that all the enzymes, hormones and the like would be in the homogenates as they were in whole animals and the fact that the reference did not use intact animals instead of homogenates when looking at individual tissues is allegedly instructive that the use of intact animals would not have been obvious for individual tissues and that the omission of intestinal tissue would have been non-obvious as this is allegedly critical for determining oral bioavailability (Remarks, Pg. 6, Lines 22-28 and Pg. 7, Lines 1-2).

This is not found to be persuasive for the following reasons, in response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See In re McLaughlin, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). Applicant's assertion that it is far less trouble to use tissue homogenates instead of intact animals is not disputed.

However, it is well known in the art that tissue or in vitro assays are subsequent to in vivo or whole animal assays and that the performance of assays in the complex environment of a whole body provides more information than that performed in a tissue homogenate. Therein lies the motivation for performing the assay in intact animals. If Applicant's assertion that all the enzymes, hormones and so forth are all present in the tissue and there is no need to use intact animals is correct, then why does Applicant's invention require the use of whole animals? Clearly they are unnecessary if Applicant's argument is taken at face value. The fact that the reference did not use intact animals instead of homogenates when looking at individual tissues does not change the fact that one of ordinary skill in the art would have found that the use of intact animals would have been obvious for individual tissues when taking the teachings of the reference as a whole. Applicant's assertion that the omission of intestinal tissue would have been non-obvious as this is allegedly critical for determining oral bioavailability is not found to be persuasive as Shaw et al. teaches the administration of the prodrug PMPA to plasma and to tissue homogenates of liver, tissues other than intestine.

The Applicant argues that there is no reason to combine the Shaw et al. and Glazier et al. references because Glazier et al. compared the activity of test compounds in paired infected and uninfected cells from the same tissues and Shaw et al. was looking at prodrug stability in individual tissues and were not concerned with whether the parental drug had antiviral activity in the various tissues as this was already known and that combining these references would result in a method testing stability of prodrugs in infected and uninfected tissue homogenates and that there is no reason to drop the intestinal homogenate as it is central to the Shaw et al. reference (Remarks, Pg. 7, Lines 10-21).

This is not found to be persuasive for the following reasons, in response to applicant's argument that Shaw et al. and Glazier et al. are nonanalogous art, it has been held that a prior art reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the applicant was concerned, in order to be relied upon as a basis for rejection of the claimed invention. See In re Oetiker, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). In this case, the two references are directed to similar fields of endeavor.

As discussed above, it is inherent in the method of Shaw et al. that the screening method would determine the relative antiviral activity conferred by the PMPA prodrug in the target and non-target tissues because PMPA is a known potent antiviral compound and the determination of the biological stability and bioavailability of prodrug derived PMPA in various tissues would necessarily also provide a determination of the relative antiviral activity of the prodrug in those tissues even if no virus were present in the tissues. The Glazier et al. reference is also directed to screening PMEA prodrugs for antiviral activity in infected and non-infected tissue. Therefore both references share a common field of endeavor, which is the characterization of the relative antiviral activity of methoxyphosphonate nucleotide analogue prodrugs in tissue. Applicant's assertion that the omission of intestinal tissue would have been non-obvious as this is allegedly

critical for determining oral bioavailability is not found to be persuasive as Shaw et al. teaches the administration of the prodrug PMPA to plasma and to tissue homogenates of liver, tissues other than intestine.

The Applicant argues that Starrett et al. does not teach or suggest omitting the intestinal homogenate of Shaw et al. and that the only difference between Shaw et al. and Starrett et al. is that Starrett et al. measured bioavailability in urine rather than plasma. Applicant alleges that this teaches away from the Examiner's argument that it would have been obvious to use whole blood rather than plasma (Remarks, Pg. 8, Lines 9-16).

This is not found to be persuasive for the following reasons, as Applicant readily admits the Starrett et al. reference was brought in solely for its teaching directed to Claims 8 and 17, and as discussed above Shaw et al. already teaches the use of blood plasma and reasons for the obviousness of using whole blood in the method of Shaw et al. were also discussed above. One of ordinary skill in the art would have been motivated to make this combination because Shaw et al. already teaches wherein the target tissue was hematological and the activity was antiviral and combination of the method of Starrett et al. which teaches the use of the aryl ester prodrug of PMEA would provide an assessment of the relative antitumor activity in both the target tissue (blood) and non-target tissues (liver and intestine). This does not constitute a teaching away as the reference was brought in for its teachings of an aryl ester phosphonoester with antitumor activity.